P-3639P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Maino *et al.*
Serial No.	:	08/803,702 Confirm. No.: 9092
Filed	:	February 21, 1997
For	:	METHOD FOR DETECTING T CELL RESPONSE TO SPECIFIC ANTIGENS IN WHOLE BLOOD
Group Art Unit	:	1644
Examiner	:	Gerald R. Ewoldt, Ph.D.

Atlanta, GA

Hon. Commissioner for Patents
Washington, D.C. 20231

SECOND DECLARATION OF JOHN D. ALTMAN, Ph.D.
UNDER 37 C.F.R. § 1.132

Sir:

I, JOHN D. ALTMAN, Ph.D., declare and state as follows:

1. This is my second declaration in support of the above-referenced patent application. My credentials as of November 2000 are presented in my first declaration; my credentials as updated to December 2001 are presented in the *curriculum vitae* attached hereto as Exhibit A.

2. I stated in my first declaration that I have devoted considerable effort to problems that require the identification and enumeration of antigen-specific T cells, and that my laboratory routinely uses flow cytometric measurement of intracellular cytokine synthesis, as well as MHC tetramer staining, in these efforts. That continues to be the case. For example, since I signed my first declaration I have published on the role of CD28-B7 interactions in the generation and maintenance of CD8 T cell memory, demonstrating that CD28 signaling is not necessary for the proliferative renewal and maintenance of memory CD8 T cells. In that work, we used both intracellular IFN-γ expression and tetramer staining to visualize and quantitate virus-specific T cell responses.[1] I have also recently published a study on the role of p53 in regulating antiviral T cell responses; in that study as well we used both MHC class I tetramers and intracellular staining for IFN-γ to enumerate antigen-specific T cells.[2]

3. I have again been asked to address the question whether the methods for detecting antigen-specific T cells described and claimed in the above-referenced patent application would have been obvious in late 1996 and early 1997 to those of ordinary skill in the art.[3]

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[1] Suresh *et al.*, *J. Immunol.* 167:5565-73 (2001) (attached hereto as Exhibit B).

[2] Grayson *et al.*, *J. Immunol.* 167:1333 - 1337 (2001) (attached hereto as Exhibit C).

[3] As I noted in my first declaration, I would say that such hypothetical person of ordinary skill has an advanced degree, such as a Ph.D., if not further postdoctoral

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4. In my first declaration, I had stated that "the methods described and claimed in the instant application revolutionized the field of cellular immunology, solving a long-sought but unmet need. Nothing in the art of which I was personally aware at the time, and nothing certainly in the references cited by the patent Examiner, would have suggested or motivated the line of inquiry pursued by Skip Maino and Louis Picker; nothing in my own experience, and nothing certainly in the references cited by the patent Examiner, would have intimated that such an approach would be attended by a reasonable expectation of success. Indeed, much of the art taught away from the present invention, rendering the results all the more surprising."

5. The "references cited by the Examiner" to which my earlier comments had been directed were Picker *et al.*,[4] Lolli *et al.*,[5] and Lolli *et al.*[6] I understand that the Examiner has now withdrawn that earlier rejection and

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training, in some aspect of immunology, notably cellular immunology, and who has experience in culturing and enumerating lymphocytes.

[4] Picker *et al.*, "Direct Demonstration of Cytokine Synthesis Heterogeneity Among Human Memory/Effector T Cells by Flow Cytometry," Blood 86(4):1408 - 1419 (1995) (hereinafter, "Picker").

[5] Lolli *et al.*, *FEMS Immunol. Med. Microbiol.* 7:55 - 62 (1993).

[6] Lolli *et al.*, *AIDS Res. Hum. Retrovir.* 10(2):115 - 120 (1994).

that the current obviousness rejection is based upon three different references: Maino *et al.*,[7] "Application Note 1",[8] and U.S. Patent No. 6,143,299. Having reviewed these three new references and the Examiner's discussion of the references in the office action mailed August 31, 2001, I would say that although Maino *et al.* could possibly have been read to suggest that certain ***steps*** of the methods of the present invention be tried, none of the references, alone or in combination, would have suggested that the claimed methods ***as a whole*** be attempted. I also reaffirm that the art of the time would have argued that any such attempt would not reasonably have been expected to succeed.

Scope and content of the prior art

6. Application Note 1 appears to be a commercial brochure that describes a reagent kit from Becton Dickinson Immunocytometry Systems (BDIS), termed the "BDIS FastImmune™ Cytokine System", that is intended for use in practicing the methods of Jung *et al.*[9] and Picker *et al.*[10], both of which are explicitly referenced in the Application Note on its first page. In the Picker *et al.*

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[7] Maino *et al.*, "FastImmune™ Assay System", Becton Dickinson Immunocytometry Systems.

[8] Becton Dickinson and Co., "Application Note 1: Detection of Intracellular Cytokines in Activated Lymphocytes".

[9] Jung *et al.*, *Immunol. Methods* 159:197 (1993) (which I understand has already been reviewed by the Examiner).

[10] Picker *et al.*, *supra*.

and Jung *et al.* methods, T cells that are activated by contact with polyclonal mitogens or superantigens are identified by flow cytometric detection of cytokines trapped within activated cells by treatment with Brefeldin A or monensin.

7. Maino *et al.* appears to be an earlier commercial brochure that describes another reagent kit from BDIS. The kit, termed the "BDIS FASTIMMUNE™ Assay System", "provides rapid analysis of individual lymphocyte subset responses to mitogenic and antigenic ligands in whole blood"[11] by flow cytometric detection and measurement of surface expression of CD69, an early activation antigen.[12]

8. U.S. Patent No. 6,143,299 describes a procedure for immunizing with relevant antigens complexed to heat shock proteins to prevent or treat tumors or infectious diseases. The patent also describes laboratory tests of the immunogenicity of the preparations (sections 5.2.5, 5.2.7, 5.8.2, 6.3), but all of these tests entail use of bulk ^{51}Cr release assays that are not capable of

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[11] Maino *et al.*, p. 2, paragraph 3.

[12] Accordingly, the two BDIS kits measure different things. This point may have been obscured by the common presence of the term "FASTIMMUNE™" in the names of both of the BDIS reagent kits. But notwithstanding the shared term, the kit earlier described in Maino *et al.* ("FASTIMMUNE™ Assay System") is designed to measure CD69 expression on the surface of activated cells, whereas the kit later described in Application Note 1 ("FASTIMMUNE™ ***Cytokine*** System") (emphasis added) is designed to measure intracellular cytokine accumulation in that small subset of $CD69^+$ activated cells that produce cytokine.

detecting MHC-restricted, antigen-specific T cells at the single cell level. The assays described are the conventional CTL assays that have been in use since the early 1970s. Because I can find absolutely nothing in this patent that is relevant to the instant application, I will not further discuss this reference in this declaration.

Differences between the prior art and claimed invention

9. I understand that the invention is now most broadly claimed as follows:

> A method of detecting T lymphocytes that are specific for a nominal antigen, comprising:
> contacting a sample containing peripheral blood mononuclear cells with a nominal antigen;
> adding to said sample an inhibitor of cytokine secretion;
> permeabilizing said cells;
> adding to said sample at least one cytokine-specific antibody; and then
> flow cytometrically detecting the intracellular binding of said cytokine-specific antibody by T cells in said sample.

10. As was recognized by the Examiner in the office action of March 27, 2000, "Picker *et al.* differs from the instant methods by using polyclonal activators or superantigen stimulation," rather than nominal antigen. So too do the methods set forth in Application Note 1, which is based on Picker *et al.*: as can be seen, the only activating agents listed in the Application Note under the heading "Reagents used in activation" are phorbol 12-myristate 13 acetate (PMA), ionomycin (I), and Staphylococcal enterotoxin B.

11. Maino *et al.* does not describe the measurement of intracellular cytokines, and accordingly does not describe the use of inhibitors of cytokine secretion.

12. In contrast to Application Note 1, however, Maino *et al.* does describe stimulation with nominal antigen. For example, Maino *et al.* states that "multiparameter flow cytometric analysis of early-activation antigen expression allows monitoring of the responses of individual subsets to antigens and mitogens,"[13] and that "[t]he FASTIMMUNE Assay System promises to be a powerful research tool for answering basic biological questions in a broad range of applications . . . [including] T-cell subset responses to viral and bacterial antigens."[14]

Lack of Motivation and Reasonable Expectation of Success

13. I understand from the most recent office action that it is Maino *et al.*'s suggestion that nominal antigen can be used to activate T lymphocytes, the T lymphocytes thereafter to be detected by flow cytometry, that provides the basis for the Examiner's argument that "the Maino *et al.* reference provides a sufficient

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[13] Maino *et al.*, p. 3.

[14] Maino *et al.*, p. 4.

expectation of success" as to have rendered the present invention as a whole obvious.

14. I disagree.

15. The critical distinction to be made is that the Maino *et al.* method looks to surface expression of CD69, not intracellular expression of cytokines, to report T cell activation. The early activation antigen **CD69 is not a cytokine, and its expression is not coextensive with expression of cytokines among T cells exposed to an activating stimulus**.

16. Picker *et al.* make this very clear, commenting that:

> **despite the fact that essentially all PMA+I-treated T cells showed marked upregulation of CD69 (see Fig 1), which is consistent with universal activation, only a subset of T cells produced detectable cytokine** at any given time point (Figs 1 and 2).[15]

Picker *et al.* figure 3 demonstrates that only 1.8% of CD4+ cells that express CD69 after contact with superantigen stimulation could be shown to express IL-4; only 11.2% of the activated cells that express CD69 express γ-IFN; and only 16.8% of such $CD69^{+}CD4^{+}$ cells expressed IL-2.

17. I do not know why far more cells express CD69 than express cytokines after contact with an activating stimulus. One possibility is that there is a

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[15] Picker *et al.*, p. 1411, first column (emphasis added).

bystander effect, in which cells that are not themselves specifically activated are nonetheless caused to express CD69 by proximity to a cell that is specifically activated. If this is the case, then measuring CD69 expression would substantially overestimate the frequency of antigen-specific cells in these assays. Another possibility is that the threshold for triggering cytokine expression is higher, and is met only in a subset of the $CD69^+$ T cells. Whatever the reason, however, the data are clear: only a fraction of cells that expression CD69 on their surface after *in vitro* contact with an activating stimulus express cytokines.

18. Thus, although Maino *et al.* could perhaps have been read to suggest that T cells activated by contact with nominal antigen *in vitro* could thereafter be identified by their surface expression of CD69,[16] that is not to say that Maino *et al.* could be, or would have been, read to suggest that the far smaller subset of T cells that

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[16] I would add that I probably would even have viewed such representations with some skepticism, given that none of ***the figures*** in Maino *et al.* examine antigen-stimulated T cells, and the language used with respect to nominal antigens is often conditional: "offer the potential"; "[i]n addition to ease of use, the measurement of early events of T-lymphocyte activation in whole blood may represent a more physiological response to nominal stimuli"; "[t]he FastImmune Assay System promises to be a powerful research tool for answering basic biological questions in a broad range of applications". I think that I would also have found significant the fact that the "Summary" table on page 11, which contains a long list of the advantages of the FastImmune Assay System, contains no mention of detecting antigen-specific cells, and that the section on "Potential Future Directions" on page 12 also contains no mention of detecting antigen-specific cells.

are truly specific for nominal antigen could be identified by flow cytometric measurement of their cytokine expression.

19. Indeed, I believe it would not have been so read, because the data in the art of the time had taught that the percentage of T lymphocytes in a peripheral blood sample that would be expected to respond specifically to a nominal antigen would be exceedingly low.

20. For example, the Lolli *et al.* references, earlier cited by the Examiner, which seem representative of ELISPOT reports in the art of the time, report the median frequency of antigen-specific T cells to be on the order of 0.01% of PBMC (about 10 IFN-γ secreting T cells per 10^5 PBMC). There is, furthermore, substantial *in vitro* clonal expansion in the methods described by Lolli *et al.* Assuming a doubling time of about 12 hours, Lolli's 72 - 96 hour incubation effects an expansion of about 50 to 150 fold in antigen-specific T cells prior to detection, suggesting that the percentage of antigen-specific T lymphocytes present in a peripheral blood sample could be on the order of one in a million PBMC. At these frequencies, antigen-specific T lymphocytes would not have been expected readily and reliably to have been detected using flow cytometric measurement of intracellular cytokines.

21. Other prior art assays, particularly limiting dilution assays ("LDA"), had also suggested that the percentage of T cells that would respond to nominal antigen would low, far too low reliably to be detected in

the Picker *et al.* (and equally, Application Note 1) intracellular cytokine assay.

22. We now know, based in part upon use of the very assay claimed in the instant application, and based in part also upon use of our tetramer assay, that LDA substantially underestimates the number and percentage of antigen-specific T cells. Although we may have suspected that LDA provided an underestimate, we did not then suspect the magnitude of such undercounting. I think that it is quite telling that Peter Doherty entitles his 1998 *Current Opinion* review "***The New Numerology*** of Immunity Mediated by Virus-Specific $CD8^+$ T Cells".

Conclusion

23. In summary, nothing in Maino *et al.*, which speaks to the detection of CD69 surface expression, alters my earlier conclusion, that those of ordinary skill in the art of cellular immunology would have been ***dissuaded*** by the poor expectation of success from attempting to detect antigen-specific T lymphocytes by *in vitro* contact with nominal antigen, followed by flow cytometric detection of intracellular cytokine expression. Nothing in Application Note 1, which advertises reagents for use in the Picker *et al.* methodology, alters my earlier conclusion, that those of ordinary skill in the art of cellular immunology would have been ***dissuaded*** by the poor expectation of success from attempting to detect antigen-specific T lymphocytes by *in vitro* contact with nominal antigen, followed by flow cytometric detection of intracellular cytokine expression.

24. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and may jeopardize the validity of the application or any patent that issues thereon.

1/28/2002
Date

John D. Altman, Ph.D.

EMORY UNIVERISTY SCHOOL OF MEDICINE
STANDARD CURRICULUM VITAE

Revised: 12/10/01

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3. **Email Address:** altman@microbio.emory.edu

4. **Birth Date and Place:** October 6, 1962 Detroit, Michigan

5. **Citizenship:** United States

6. **Current Titles and Affiliations:**

   a. **Academic Appointments:**

      i. **Primary Appointments:**
      Assistant Professor of Microbiology and Immunology
      Emory University School of Medicine (January 1997-present)

      ii. **Joint and secondary appointments:**
      Affiliate Scientist, Emory Vaccine Center (January 1997-present)
      Affiliate Scientist, Yerkes Regional Primate Center of Emory University (1997-present)

      iii. **Other Administrative Appointments**
      Director, Emory Vaccine Center Flow Cytometry Facility, 1998-present

7. **Previous Administrative Appointments**
Interim Director, Emory University School of Medicine Flow Cytometry Core Facility, 2001

8. **Education:**
Massachusetts Institute of Technology
Degree: SB. in Chemistry
September 1980- June 1984
Research Supervisor: Dr. Michael A. Marletta

University of California, San Francisco
Degree: PhD. in Pharmaceutical Chemistry 1991
Thesis title: Engineering of Bovine Pancreatic Trypsin Inhibitor for NMR and Protein Folding
Supervisor: Dr. Irwin D. Kuntz

9. **Postgraduate Training:**
Post Doctoral Fellow, Stanford University, Laboratory of Dr. Mark Davis, September 1991-December, 1996

10. Committee Memberships:

a. National and International:

- Ad hoc member, National Institutes of Health, Biological and Physiological Sciences Special Emphasis Panel Study Section, December 16, 1997
- Ad Hoc Reviewer, National Cancer Institute Laboratory of Biochemistry intramural research program, FY1998.
- Panel Member, Strategic Planning Meeting for NIH Vaccine Research Center, Washington, D.C. April 16-17, 1999.
- Panel Member, NIH-sponsored MHC Tetramer Workshop, Bethesda, MD April 22, 1999.
- Panel Member, NCI/NIAID-sponsored Workshop on Infectious Etiologies of Chronic Diseases, Rockville, MD. June 13-14, 1999.
- Ad hoc grant reviewer for The Council for Medical and Health Research of The Netherlands Organisation for Scientific Research (CMHR), December 21, 1999.
- Member, Ad Hoc Working Group on Cellular Immunogenetics of Nonhuman Primates, 1999-present.
- Ad hoc member, National Institutes of Health, AIDS and Related Research 2 (NIH - AAR2) Study Section Ad Hoc July 13-14, 2000.
- Ad hoc member, National Institutes of Health, Allergy and Immunology (NIH - ALY) Study Section October 18-19, 2001.

b. Institutional:

- Faculty search committee, Assistant Professor in Virology, Department of Microbiology and Immunology, 2000.
- Microbiology and Immunology Departmental Retreat Committee, 2000-2001.
- Flow Cytometry Core Director Search Committee, 2001.

11. Consultantships:

- Beckman/Coulter Corporation, 1997-present
- St. Jude Childrens Medical Center, 1999-present

12. Editorships and Editorial Boards:

- Virology (editorial board), 2000-present

13. Manuscript Reviewer:

- Cellular Immunology
- Immunity
- International Immunology
- Journal of Immunology
- Journal of Virology
- Tissue Antigens
- Virology

14. Honors and Awards:

- Pew Scholar in the Biomedical Sciences 1999-2003
- Post Doctoral Fellow of the American Cancer Society -- 1991-1994
- University of California Regents Fellow -- 1987-1988
- National Science Foundation Graduate Fellow -- 1984-1987

- Phi Beta Kappa -- MIT 1984
- American Institute of Chemists Student Award -- 1984
- University of Michigan Regents Scholarship – 1980

15. Society Memberships:

- American Association of Immunologists, 1998-present.
- American Association for the Advancement of Science.
- International Society for Analytical Cytology.

16. Organization of National or International Conferences:

- Conference Symposium Chair, Autumn Immunology Conference, Chicago, IL, October 1999

17. Research focus

The research of my laboratory is focused upon the induction, function, trafficking, and regulation of antiviral T cell immune responses. We pursue studies in mouse, nonhuman primate, and human models, with the ultimate goal of developing principles and applications that result in improved vaccines for humans.

18. Patents

- "Compositions and Methods for the Detection, Quantitation, and Purification of Antigen-Specific T Cells." Altman, John; McHeyzer-Williams, Michael; Davis, Mark M. (5,635,363).

19. Visiting scholars trained in MHC tetramer technology

- Dr. Conni Bergmann (UCLA).
- Dr. Kirsten Flynn (St. Jude Children's Research Hospital, laboratory of Dr. Peter Doherty).
- Dr. Edward Usherwood (St. Jude Children's Research Hospital, laboratory of Dr. David Woodland).
- Weidong Xie (St. Jude Children's Research Hospital, institutional tetramer core facility).
- Philippe Bousso (Institut Pasteur, laboratory of Dr. Philippe Kourilsky).
- Scottie Adams (Trudeau Institute, institutional tetramer core facility).
- Karen Anderson (Harvard University, laboratory of Dr. Lee Nadler, Dana Farber Cancer Institute).
- Jan Christensen (The Panum Institute, Denmark).
- Jana Subrtova (Institute of Hematology and Blood Transfusion, Czech Republic).
- Mark Wills (Addnbrooke's Hospital, Cambridge, U.K., laboratory of Dr. Patrick Sissons).
- Dr. Jung-Chung Lin (Professor and Chairman, Department of Microbiology and Immunology, Tzu Chi University, Taiwan)
- Sandra Aung (Vanderbilt University, laboratory of Dr. Barney Graham).
- Aki Hoji (University of Pittsburgh, laboratory of Dr. Charles Rinaldo).

20. Lectureships, Seminar Invitations, and Visiting Professorships:

1. "Beyond Phenotypic Analysis of Antigen-Specific T Cells", Emory, UCLA, and ADARC joint symposium on HIV Vaccine Development., June 26, 2001.

2. "Beyond Phenotypic Analysis of Antigen-Specific T Cells", Institute of Human Virology Meeting on Immune Reconstitution & Surrogate Markers in HIV/AIDS", April 28, 2001.
3. "MHC Tetramer Analyses of Vaccine Induce Responses", International AIDS Vaccine Initiative Workshop on T Cell Immune Responses, January 17, 2001.
4. "Induction of $CD8^+$ T Cell Responses by Heterologous Prime-Boost", MCP-Hahnemann, December 19, 2000.
5. "Induction of $CD8^+$ T Cell Responses by Heterologous Prime-Boost", University of Pennsylvania, December 18, 2000.
6. "Induction of $CD8^+$ T Cell Responses by Heterologous Prime-Boost", Third International Summit Meeting on "Immunological Correlates of Protection from HIV Infection and Disease", Sestri-Levante, Italy, December 3, 2000
7. "Direct Analysis of Antigen-Specific $CD8^+$ T Cell Responses by MHC Tetramer Staining", 15th Annual Clinical Applications of Cytometry Meeting, Austin, Texas, November 15, 2000.
8. "MHC tetramer-based analyses of HIV-specific T cell responses", Frontiers in HIV Cytometry – a tribute to Janis Giorgi, 15th Annual Clinical Applications of Cytometry Meeting, Austin, Texas, November 12, 2000.
9. "Generation and Maintenance of Antigen-Specific $CD8^+$ T Cell Memory", Case Western Reserve University, October 24, 2000.
10. "MHC Tetramers for Analysis of T Cell Immune Responses", 26^{th} Annual Meeting of the American Society for Histocompatibility and Immunogenetics, Orlando, Florida. October 14, 2000.
11. "MHC Tetramers", Annual Symposium on Nonhuman Primate Models for AIDS, Madison, Wisconsin, October 7, 2000.
12. "Evaluation of HIV-vaccine Induced $CD8^+$ T Cell Responses by MHC Tetramers", Plenary session of the HIV Vaccine Trials Network Meeting, San Francisco, CA, October 4, 2000.
13. "Induction of $CD8^+$ T Cell Responses by Heterologous Prime-Boost", The 2^{nd} Edward Jenner Institute for Vacccine Research Conference on Fundamental Issues in Vaccine Immunity, Oxford, England, September 14, 2000.
14. "The Kinetics of Antiviral T Cell Immune Responses." American Association of Immunologists Annual Meeting, May 13, 2000.
15. "Vaccine induced T cell immune responses in rhesus macaques." University of Toronto, March 7, 2000.
16. "The Kinetics of Antiviral T Cell Immune Responses." Keystone Meeting on "Cell Biology of Virus Entry, Replication and Pathogenesis", March 3, 2000.
17. "Preparation and use of MHC Tetramers" Workshop Meeting of the European Concerted Action 'Correlates of Protective Immunity to HIV Infection And Disease' Group, Würzburg, Germany, February 14-16, 2000.
18. "Quantitative Analysis of Antiviral T Cell Responses." Rush Presbyterian Medical College, Chicago, IL, January 17, 2000.

19. "Quantitative Analysis of Antiviral T Cell Responses." Harvard Medical School. December 10, 1999.

20. "Quantitative Analysis of Antiviral T Cell Responses." Autumn Immunology Conference, Chicago, IL October 21, 1999.

21. "Application of tetramer technology in the rhesus macaque", Office of AIDS Research/NCRR Workshop on "MHC Typing Issues and Breeding of Genetically Defined Nonhuman Primates for AIDS Vaccine Studies." Bethesda, MD, August 24, 1999.

22. "Direct ex vivo analysis of antigen-specific T cell responses", NCI/NIAID Workshop on Infectious Etiologies of Chronic Diseases, Rockville, MD, June 14, 1999.

23. "Quantitative Analysis of Antiviral T Cell Immune Responses." Medical College of Georgia, Augusta, GA, May 20, 1999.

24. "The New Math of Antiviral T Cell Responses", 1999 Viruses and Cells Gordon Conference, Il Ciocco, Italy, May 6, 1999.

25. "The MHC Tetramer Core Facility." NIAID Workshop on MHC Tetramers, Washington, DC, April 22, 1999.

26. "Direct quantitation of cellular immune responses to HIV: New tools to study antiviral immune responses and guide HIV vaccine development." American Federation for Medical Research (part of the 1999 FASEB meeting), Washington DC, April 21, 1999.

27. "Quantitative Analysis of Antiviral CD8+ T Cell Responses." Wake Forrest University, April 8, 1999.

28. "What are the T cells stained by tetramers", Novartis Foundation Discussion Meeting, London, March 12, 1999.

29. "T Cell Memory", Symposium Chair, Royal Society Meeting, March 11, 1999.

30. "Analysis of cross-reactivity in antigen-specific $CD8^+$ T cells by analysis of peptide-stimulated intracellular IFN□ production and staining with MHC tetramers," NIH Workshop on Assessing Cytokine Responses in Vaccinated Macaques, Rockville, MD, February 11, 1999.

31. "Defining T Cell Memory", Epimmune, January 27, 1999.

32. "Defining T Cell Memory", The Scripps Research Institute, January 26, 1999.

33. "Defining T Cell Memory", Plenary session presentation at Keystone Conference, Joint Meeting on HIV Vaccine Development and AIDS Pathogenesis, January 8, 1999.

34. "Massive CD8+ T Cell Responses to Viral Infections", August 21, 1998, International Symposium on The Major Histocompatibility Complex: From Genes to Function. Queensland, Australia.

35. "The New Math of Antiviral T Cell Responses" St. Jude Children's Hospital, Memphis Tennessee, July 13, 1998.

36. "The New Math of Antiviral T Cell Responses" July 27, 1998, Merck Laboratories.

37. "Direct Identification of Antigen-Specific T Cells" October 19, 1997, American Society for Histocompatibility and Immunogenetics.

38. "Evaluation of HIV Specific $CD8^+$ T Cell Responses by Staining with MHC Tetramers" July 21, 1997, AIDS Clinical Trials Group Meeting.

39. "Direct Identification of Antigen-Specific T Cells" May 5, 1997, National Cooperative Vaccine Development Group Conference, National Institutes of Health.

40. "Direct Identification of Antigen-Specific T Cells" February 19, 1997, Merck Laboratories.

21. Bibliography:

Published and accepted research articles (clinical, basic science, other) in refereed journals:

1. Crespi, C. L., **Altman, J. D.** & Marletta, M. A. (1985). "Xenobiotic metabolism and mutation in a human lymphoblastoid cell line." *Chem. Biol. Interact.*, **53**, 257-71.

2. Collins, S., **Altman, J. D.** & Marletta, M. A. (1985). "Development of an affinity chromatography resin for the purification of carcinogen binding proteins from mouse liver." *Biochem. Biophys. Res. Commun.*, **129**, 155-62.

3. **Altman, J.**, Lipka, J. J., Kuntz, I. & Waskell, L. (1989). "Identification by proton nuclear magnetic resonance of the histidines in cytochrome b5 modified by diethyl pyrocarbonate." *Biochemistry*, **28**, 7516-23.

4. Guiles, R. D., **Altman, J.**, Kuntz, I. D., Waskell, L. & Lipka, J. J. (1990). "Structural studies of cytochrome b5: complete sequence-specific resonance assignments for the trypsin-solubilized microsomal ferrocytochrome b5 obtained from pig and calf." *Biochemistry*, **29**, 1276-89.

5. **Altman, J. D.**, Henner, D., Nilsson, B., Anderson, S. & Kuntz, I. D. (1991). "Intracellular expression of BPTI fusion proteins and single column cleavage/affinity purification by chymotrypsin." *Protein. Engin.*, **4**, 593-600.

6. Driscoll, P. C., **Altman, J. D.**, Boniface, J. J., Sakaguchi, K., Reay, P. A., Omichinski, J. G., Appella, E. & Davis, M. M. (1993). "Two-dimensional nuclear magnetic resonance analysis of a labeled peptide bound to a class II major histocompatibility complex molecule." *J. Mol. Biol.*, **232**, 342-50.

7. **Altman, J. D.**, Reay, P. A. & Davis, M. M. (1993). "Formation of functional peptide complexes of class II major histocompatibility complex proteins from subunits produced in Escherichia coli." *Proc. Natl. Acad. Sci. U.S.A.*, **90**, 10330-4.

8. **Altman, J. D.**, Moss, P. A. H., Goulder, P. J. R., Barouch, D. H., McHeyzer-Williams, M. G., Bell, J. I., McMichael, A. J. & Davis, M. M. (1996). "Phenotypic analysis of antigen-specific T lymphocytes." *Science*, **274**, 94-96.

9. Reich, Z., **Altman, J. D.**, Boniface, J. J., Lyons, D. S., Kozono, H., Ogg, G., Morgan, C. & Davis, M. M. (1997). "Stability of empty and peptide-loaded class II major histocompatibility complex molecules at neutral and endosomal pH: comparison to class I proteins." *Proc. Natl. Acad. Sci. U. S. A.*, **94**, 2495-500.

10. Crowley, M. P., Reich, Z., Mavaddat, N., **Altman, J. D.** & Chien, Y. (1997). "The recognition of the nonclassical major histocompatibility complex (MHC) class I molecule, T10, by the gammadelta T cell, G8." *J. Exp. Med.*, **185**, 1223-30.

11. Murali-Krishna, K., **Altman, J. D.**, Suresh, M., Sourdive, D. J. D., Zajac, A. J., Miller, J. D., Slansky, J. & Ahmed, R. (1998). "Counting Antigen-Specific CD8 T Cells: A Reevaluation of Bystander Activation during Viral Infection." *Immunity*, **8**, 177-187.

12. Flynn, K. J., Belz, G. T., **Altman, J. D.**, Ahmed, R., Woodland, D. L. & Doherty, P. C. (1998). "Virus-specific $CD8^+$ T cells in primary and secondary influenza pneumonia." *Immunity*, **8**, 683-691.

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